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(54) **Hautwirksame Pharmaka mit Liposomen als Wirkstoffträger.**

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PHARMAZIE, Band 39, Nr. 9, September 1984,
Seiten 627-629, Ost-Berlin, DD; L.
KROWCZYNSKI et al.: "Liposomen als Wirk-
stoffträger in der percutanen Therapie"

CHEMICAL ABSTRACTS, Band 93, Nr. 2, 14.
Juli 1980, Seite 314, Zusammenfassung Nr.
13043m, Columbus, Ohio, US; M. MEZEL et al.:
"Liposomes - a selective drug delivery sy-
stem for the topical route of administration.
I. Lotion dosage form", & LIFE SCI. 1980,
26(18), 1473-7

CHEMICAL ABSTRACTS, Band 80, Nr. 5, 4.
Februar 1974, Seite 45, Zusammenfassung
Nr. 22841d, Columbus, Ohio, US; L.B. FISHER
et al.: "Topical antipsoriatic agents and epi-
dermal mitosis in man", & ARCH. DERMA-
TOL. 1973, 108(3), 374-7

ROTE LISTE, 1983, Editio Cantor,
Aulendorf/Württ., DE

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Beschreibung

Die Erfindung betrifft Medikamente zur Therapie von Erkrankungen der Haut, die gegebenenfalls schon an sich für die Behandlung von Hautkrankheiten bekannte Wirkstoffe enthalten, und die als Externa im Bereich der erkrankten Hautstelle angewendet werden.

Zur Lokaltherapie von Hautkrankheiten werden in der Regel Salben, Cremes, Lotionen oder Tinkturen verwendet, in die bestimmte Wirkstoffe eingearbeitet sind. Für den therapeutischen Effekt dieser Wirkstoffe ist Voraussetzung, daß sie aus der entsprechenden Grundlage in ausreichender Menge freigegeben werden. Nur wenn dies der Fall ist, können die Wirkstoffe dann in die Haut eindringen und dorthin gelangen, wo ihre Wirkungsqualitäten benötigt werden.

Neuartige Arzneistoffträger sind die Liposomen. Als solche werden kugelförmige Gebilde aus einer oder mehreren Lipiddoppelschichten mit wässrigen Innenraum bezeichnet, und die sich aus Phospholipiden, z. B. Lecithin, unter anderem durch deren mechanische Feinverteilung herstellen lassen. Herstellungsweisen von Liposomen und deren Verwendung als Arzneimittel- oder Kosmetikmittelträger, wobei die Wirkstoffe in den Innenräumen der Liposomen eingelagert sind, sind in US-A 3 957 971, in DE-A 28 18 655, in DE-A 28 34 308 oder in GB-A-2 013 609 angegeben. Aus "Pharmazie in unserer Zeit" 11, (1982) 97 bis 108, ist praktisch der derzeitige Stand des Wissens bezüglich Herstellung von Liposomen und deren Anwendung als Arzneimittelträger ersichtlich. Danach sind Applikationsarten wie intravenöse, intramuskuläre und subcutane Injektionen und auch orale Verabreichungen von arzneimittelhaltigen Liposomen getestet worden. Prüfungen von medikamentösen Formulierungen mit Liposomen als Träger zu lokalen Anwendungen auf der Haut, z. B. bei Hautkrankheiten, standen möglicherweise Vorurteile infolge der Kenntnisse des Hautaufbaues und die vielfältigen Erfahrungen mit Applikationen auf der Haut entgegen, da in der Epidermis unter dem Stratum corneum, der die Oberfläche der Haut bildenden Hornschicht, eine dichter gebaute Zellage, das Stratum conjunctum oder compactum, liegt, deren Funktion die Erschwerung bzw. Verhinderung der Penetration von Stoffen von außen ist.

Auch Pharmazie, Bd. 39, 9/1984, 627-629, beschreibt "Liposomen als Wirkstoffträger in der percutanen Therapie", für Triamcinolon als Modellsubstanz mit drei- bis viermal höherer Resorption percutan.

Die am häufigsten verwendeten Wirkstoffe zur äußeren Behandlung von Hautkrankheiten sind Kortikosteroide und Trihydroxianthracene. So beschreibt die Rote Liste 1983 unter Nr. 31 370 Psoradexan®-Creme (Dithranol/Harnstoff) zur Anwendung bei subakuter und chronischer Psoriasis. Wegen ihres geringen Penetrationsvermögens durch die Haut nach Liberation aus den Trägergrundlagen, müssen diese Stoffe, um einen ausreichenden therapeutischen Effekt zu erzielen in hoher Konzentration und in hohem Überschuß in z. B. Salben oder Cremes vorliegen.

Aufgabe und Gegenstand der Erfindung

Es war daher Aufgabe der Erfindung hautwirksame Pharmaka zu finden, mit denen die Wirkstoffe schneller in die Haut dringen bzw. diese durchdringen können, um so Medikamente zur Verfügung zu haben, die die Wirkungssubstanzen ständig und in ausreichender Menge an den Wirkort geben.

Hautwirksame Stoffe, wie z. B. Kortikosteroide oder Anthracentriole, lassen sich relativ einfach mit Liposomen kombinieren, d. h. in diese einschließen. Überraschenderweise wurde gefunden, daß mit so beladenen Liposomen, in einer streichfähigen Form z. B. als Salben oder Cremes auf die Haut gebracht, die Penetration der Wirkstoffe wesentlich schneller erfolgt als im Vergleich aus einer üblichen Wirkstoff-Salben-Formulierung.

Wie weiter gefunden wurde, läßt sich Harnstoff, von dem zur Therapie von Hauterkrankungen selbst eine ganze Reihe von Wirkungsqualitäten, z. B. als Keratolytikum, bekannt sind, vorteilhaft mit in die Liposomenpräparate einarbeiten, wobei Mischungen von Harnstoff und Hydroxanthracenen (Anthracentriole) und gegebenenfalls weiteren hautwirksamen Stoffen, wie z. B. Steroiden mit den Liposomen bzw. den Phospholipidgemischen als deren Vorstadium zu hautwirksamen Medikamenten formuliert werden.

Beispielsweise werden mit erfindungsgemäßen Harnstoff-Dithranol-Zubereitungen etwa 3 bis 4 mal höhere Wirkstoff-Haut Penetrationen als mit bisher üblichen Formulierungen gemessen. Somit ermöglichen die neuen Formulierungen erhebliche Einsparungen an Wirkstoffmengen. Durch die Mengeneinsparung werden auch andere Probleme, wie z. B. Verschmutzung von Textilien, die insbesondere bei Anwendung farbiger Substanzen oder farbiger Metabolite, wie z. B. Oxidationsprodukten der Anthracentriole, auftreten, entschärft bzw. gelöst.

Durchführung der Erfindung

Die Herstellung der erfindungsgemäß anzuwendenden Liposomenzubereitung aus den Aufbaukomponenten der Liposomen, den Phospholipiden, insbesondere den Phosphatidylcholinen, wie den Lecithinen, einer in der Natur vorkommenden Gruppe von Phospholipiden, beispielsweise Lecithin aus Sojabohnen, dem gebräuchlichsten Rohstoff zur Herstellung von Lecithin, sowie weiteren Zusatzstoffen, wie Sterinen, z. B. dem Cholesterin, und den hautwirksamen Stoffen, dem Harnstoff und den Hydroxyanthracenen, kann nach verschiedenen Methoden, wie sie beispielsweise in den oben angegebenen Literaturstellen beschrieben sind, vorgenommen werden. Das für die Herstellung der Liposomenträger anzuwendende Verhältnis der in der Lipidausgangsmischung vorhandenen Substanzen, von z. B. Lecithin zu z. B. Cholesterin, kann in den Bereichen 10 : 0,1 bis etwa 1 : 1, vorwiegend bei 10 : 1 bis 1 : 1, insbesondere bei 5 : 1 bis 2 : 1 liegen. Auch weitere Substanzen, z. B. Dialkylphosphate oder Sphingomyelin oder Hilfsstoffe wie Zucker- bzw. Aminozuckerderivate, z. B. zur Stabilisierung der Liposomenmembran, und Antioxidantien können bei der Präparierung mitverwendet werden.

Die Herstellung kann beispielsweise nach der bekannten Film-Dispersions-Methode, einer schonenden Eindampfung, z. B. im Rotationsverdampfer, der Lipid-Wirkstoff-Mischung in Chloroform-Alkohol-Lösung vorgenommen werden, welcher zur Herstellung besonders kleiner Partikel mit relativ enger Größenverteilung eine Ultraschallbehandlung nachgeschaltet werden kann. Durch Zentrifugieren und Waschen können die wirkstoffhaltigen Liposomen dann isoliert und gereinigt werden. Die Partikelgröße der nach solchen Verfahren erhaltenen Liposomen kann stark variieren und im Bereich von einem oder mehreren Micrometern bis hinunter zu etwa 10 nm liegen. Für die Verwendung als hautwirksame Pharmakaträger haben die Liposomen vorzugsweise Durchmesser von 20 bis 50 nm.

Wirkungssubstanzen, die mit den obengenannten Aufbaukomponenten der Liposomen erfindungsgemäß eine hautwirksame Pharmaka bilden, gehören z. B. der großen Gruppen der Antibiotika oder der Sulfonamide an, oder sind insbesondere solche aus der Gruppe der Kortikosteroide und Hydroxyanthracene. Die therapeutischen Wirkungen dieser Stoffe sind bekanntermaßen insbesondere bei der Behandlung entzündlicher, ekzematöser oder allergischer Hauterkrankungen angezeigt. Durch Kombination von Wirkstoffen aus den verschiedenen Substanzgruppen wird noch eine therapeutische Wirkungssteigerung erzielt. Die Verwendung von Harnstoff bei der Herstellung wirkstoffhaltiger Liposomen in Kombination mit Hydroxyanthracenen und gegebenenfalls weiter mit Kortikosteroiden, führt zu therapeutisch wertvollen Formulierungen. Die Vorteile der erfindungsgemäßen Medikamente gegenüber bekannten Medikamenten mit gleichen Wirksubstanzen, sind durch die verbesserte Penetration durch die Haut, damit einer höheren Verfügbarkeit des Arzneistoffes am Wirkort und somit einer deutlichen Senkung der anzuwendenden Wirkstoffmenge gegeben, was sich in einer Verringerung von Nebenwirkungen und wesentlichen Verbilligung des Medikaments niederschlägt.

Erfindungsgemäß einsetzbare Kortikosteroide sind beispielsweise Fludrocortison, Fluocortolon, Fluorandrenolon, Triamcinolon, Methylprednisolon; Anthracentriole, die in den erfindungsgemäßen Formulierungen eingesetzt werden, und die als Dermatica oder Antiseptika bekannt sind, sind die Hydroxyanthracene 1,8,9-Anthracentriol, auch als 1,8,9-Anthratriol bzw. 1,8-Dihydroxianthranol-(9) und unter dem von der WHO vorgeschlagenen Freinamen Dithranol bekannt, oder 1,2,10-Anthracentriol, das auch als 1,2,10-Anthratriol bekannt ist.

Auch für die transdermale Applikation von Wirkstoffen verschiedener Art bei Erkrankungen anderer Organismusteile als der Haut bzw. hautnaher Bereiche, ist die Verwendung von Medikamenten mit pharmakahaltigen Liposomen wegen deren besseren Hautpenetration und damit schnellerem Transport der Pharmaka deutlich wirkungsvoller.

Die Zubereitungen können auch noch Wirkstoffe für die beispielsweise eine Hautpenetration nicht angezeigt oder deren Penetrationsgeschwindigkeit nicht so kritisch ist, in bisher üblicher Zugabe enthalten.

Die zur äußeren Anwendung an der Haut hergestellten Zubereitungen sind disperse Systeme, die die Wirkstoff-Liposomen-Präparationen und gegebenenfalls weitere Wirkstoffe, gelöst, emulgiert oder suspendiert enthalten. Die Applikationsart der neuartigen hautwirksamen Medikamente mit pharmakahaltigen Liposomen wird im wesentlichen nach bisher bekannter Vorgehensweisen, d. h. beispielsweise als Salben oder Cremes durchgeführt.

Experimenteller Teil

1. Herstellung von Liposomen-Wirkstoff-Kombinationen

Chloroform/Äthanol 1 : 1 - oder Chloroform/Methanol 1 : 1 - Lösungen von Lecithin, Cholesterin und Wirkstoff, werden bei etwa 30 °C im Rotationsverdampfer vom Lösungsmittel unter Bildung eines dünnen Lipid-Wirkstoff-Films befreit. Anschließend wird der Film mit 8 molarer Calciumchloridlösung von 60 °C

versetzt und durch manuelles Schütteln die Ablösung der Liposomen von der Wandung erwirkt. Die so erhaltene Dispersion wird dann im Ultraschalldesintegrator weiter zerkleinert, anschließend zentrifugiert und dann die Liposomen-Wirkstoff-Kombination dreimal mit Calciumchloridlösung gewaschen.

Aus der folgenden Zusammenstellung sind die Zusammensetzungen hergestellter Liposomen in Gewichtsteilen Lecithin und Cholesterin und die von den eingesetzten Wirkstoffen Triamcinolon oder Dithranol eingebauten Anteile ersichtlich.

10	Lecithin (Gewichtsteile)		30	30	32.5	32.5	35	35
	Cholesterin (Gewichtsteile)		13	10	13	10	10	7
15	Einbau von eingesetztem	Triamcinolon (in %)	41	32.4	56.2	42.8	62.1	49.8
		Dithranol (in %)	69.7	42.1	85.6	76.1	87.5	62.1

Patentansprüche

1. Hautwirksame, pharmazeutische Zubereitung zur äußeren Anwendung auf der Haut, die im wesentlichen aus Harnstoff und mindestens einem Wirkstoff aus der Gruppe der Hydroxyanthracene besteht, dadurch gekennzeichnet, daß die Harnstoff-Hydroxyanthracen-Mischung in Liposomen eingearbeitet bzw. eingeschlossen ist.
2. Hautwirksame, pharmazeutische Zubereitung nach Anspruch 1, dadurch gekennzeichnet, daß das Hydroxyanthracen Dithranol ist.
3. Hautwirksame, pharmazeutische Zubereitung nach den Ansprüchen 1 und 2, dadurch gekennzeichnet, daß die Zubereitung neben der Harnstoff-Hydroxyanthracen-Mischung noch weitere bekannte hautwirksame Wirkstoffe in der Liposomen-Einarbeitung enthält.
4. Hautwirksame, pharmazeutische Zubereitung nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß der Zubereitung mit den in Liposomen eingeschlossenen Wirkstoffen auch Wirkstoffe in bisher üblicher Zubereitung beigegeben sind.

Claims

1. A dermatologically effective, pharmaceutical preparation for external use on the skin consisting largely of urea and at least one active substance from the group of hydroxyanthracenes, characterised in that the urea-hydroxyanthracene mixture is incorporated or enclosed in the liposomes.
2. A dermatologically effective, pharmaceutical preparation according to claim 1, characterised in that the hydroxyanthracene is dithranol.
3. A dermatologically effective, pharmaceutical preparation according to claims 1 and 2, characterised in that the preparation also has, apart from the urea-hydroxyanthracene mixture, further known dermatologically effective active substances which are incorporated in the liposomes.
4. A dermatologically effective, pharmaceutical preparation according to claims 1 to 3, characterised in that active substances as used in a hitherto conventional preparation are also added to the preparation containing active substances enclosed in the liposomes.

Revendications

1. Préparation pharmaceutique à action cutanée pour usage externe sur la peau, se composant essentiel-

lement d'urée et d'au moins une substance active du groupe des hydroxyanthracènes, caractérisée en ce que le mélange urée/hydroxyanthracène est incorporé ou inclus dans des liposomes.

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2. Préparation pharmaceutique à action cutanée selon la revendication 1, caractérisée en ce que l'hydroxyanthracène est le dithranol.
- 10
3. Préparation pharmaceutique à action cutanée selon la revendication 1 ou 2, caractérisée en ce qu'elle contient, outre le mélange urée/hydroxyanthracène, d'autres substances actives connues à action cutanée, incorporées dans des liposomes.
- 15
4. Préparation pharmaceutique à action cutanée selon l'une quelconque des revendications 1 à 4, caractérisée en ce qu'il est adjoit, à la préparation contenant les substances actives incluses dans des liposomes, des substances actives en préparation jusqu'ici classique.

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A request for correction.(part of Claim nr 1 is missing). has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 3.).

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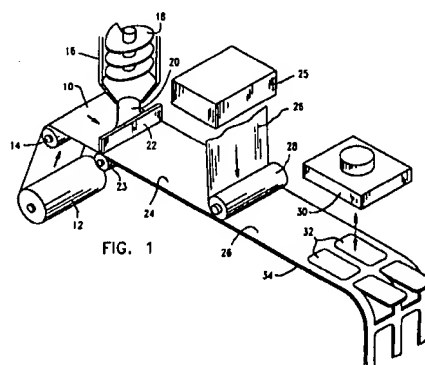
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(54) **Non-occlusive adhesive patch for applying medication to the skin.**

(57) A non-occlusive medication patch (32) to be applied to the skin includes a porous self-supporting backing layer (10) to give the patch the required integrity and strength by acting as a supporting framework for other components, and a flexible hydrophilic pressure-sensitive adhesive reservoir (20) comprising a natural or synthetic polymer for the sustained release of medication to be absorbed topically through the skin into the body of a patient. The reservoir has two portions: first, an external coating layer (24) with an exposed lower skin-contacting surface (24b) that forms a pressure-sensitive bond with the skin, and second, an upper internal portion (24a) which infiltrates the porous backing (10) and becomes solidified therein after being applied so that the reservoir and the backing are unified, enabling the backing itself to act as a storage location for the medication-containing reservoir (20). The medication within the reservoir migrates over time from within the backing (10) through the lower coating layer (24b) and passes through the skin to provide sustained release of the medication into the body of a patient.

**EP 0 674 913 A2**

FIELD OF THE INVENTION

This invention relates to a non-occlusive adhesive patch for applying medication to the skin.

5 SUMMARY OF THE INVENTION

A non-occlusive medication-containing adhesive patch is provided for being applied to the skin for releasing a medication into the body of a patient. The patch has a porous backing layer that can be formed from a fibrous material, *e.g.*, non-woven fabric. To the backing is applied a flexible pressure-sensitive
 10 adhesive, typically a hydrocolloidal gel which serves as a reservoir for the sustained release of a medication which is uniformly distributed throughout the adhesive layer. The pressure-sensitive reservoir has two portions including, an external coating layer portion with an exposed surface for bonding to the skin and an internal portion that is infiltrated within the porous backing layer. The adhesive reservoir comprises a natural or synthetic polymer and a biomedically active medication dispersed therein. The internal portion of the
 15 hydrocolloidal reservoir which infiltrates the backing is solidified within the pores and interstices within the backing so that the reservoir and the backing are unified, enabling the backing itself to act as a storage location for the medication-containing reservoir. The gel reservoir is applied as a fluid. Solidification of the gel reservoir is delayed until after the gel has been applied to the porous backing layer.

20 THE FIGURES

Figure 1 is a perspective diagrammatic view illustrating a preferred method of forming products in accordance with the invention;
 Figure 2 is a perspective view of the improved medication patch applied to the body;
 25 Figure 3 is a plan view showing the medication patch packaged within in a pouch used as a shipping package;
 Figure 4 is a cross-sectional view of the medication patch taken on line 4-4 of Fig. 3 with a portion of the liner sheet partially removed; and
 Figure 5 is a greatly enlarged microscopic view of the medication patch and liner sheet taken on line 5-5
 30 of Fig. 4.

DETAILED DESCRIPTION OF THE INVENTION

Refer now to Fig. 1 which illustrates diagrammatically the production of medication-applying patches in
 35 accordance with the invention. The backing sheet 10 is unwound continuously from a supply roll 12, passes upwardly in the figure over an idler roll 14 and then travels horizontally beneath a continuous processing mixer 16 where freshly prepared fluid hydrogel material at 20 is applied to the upper surface of the backing sheet 10.

The backing 10 is a porous self-supporting sheet of water insoluble polymeric material that provides
 40 strength and integrity for the adhesive patch as well as acting as a substrate for receiving and retaining a portion of the liquid hydrogel as will be described below.

One preferred backing sheet 10 is a lightweight, pliable strip composed, for example, from a nonwoven fabric which consists of polymeric fibers such as polyester, cotton or cellulose fibers bonded together with a
 45 sizing resin. The backing sheet 10 should be nonirritating to human skin. If desired, the backing sheet 10 can be coated on its back surface with a release coating such as a silicone release coating as described in patent 4,696,854 which is incorporated herein by reference. One suitable release coating is a 100% solids electron beam curable silicone such as Tego® Resin Acrylates/RC-Series RC 705 and RC 726 by Goldschmidt Chemical Corporation of Hopewell, Virginia. The preferred backing sheet 10 is a porous polymeric water insoluble nonwoven fibrous fabric. A suitable sizing material for bonding the fibers together
 50 is a latex resin.

The backing sheet 10 can comprise other stable, water insoluble flexible sheet materials. One preferred backing comprises a 0.14 mm strip of nonwoven fabric formed from a mixture of cellulose fibers derived from wood pulp and polyester fibers. The fibers are assembled loosely into the backing to maintain porosity. A unifying or sizing resin is applied to hold the fibers together. The sizing resin can comprise a
 55 nonirritating resin applied as a latex emulsion. One example is Hycar® 26477, a resin produced by B.F. Goodrich Co. of Brecksville, Ohio. Another suitable backing sheet is a nonwoven fabric comprising a wetlay cellulose and polyester nonwoven fabric containing as a sizing an acrylic latex emulsion resin, *e.g.*, product number N7601 by Dexter Corporation of Windsor Locks, Connecticut.

In another embodiment of the invention, the backing sheet 10 comprises a porous woven 0.12 mm acetate polymer cloth sometimes known as "silk cloth." Another form of backing sheet 10 is an open-cell plastic foam strip of low density polyethylene or polyvinyl acetate resin. Other backing sheets that can be used include woven cotton cloth or other cloth formed from a synthetic polymer. Suitable synthetic cloths include nylon, polyester, polyacetate. When the backing sheet 10 is a woven cloth, no sizing resin is needed. The backing sheet 10 is pervious to air so that the patch is non-occlusive to the skin.

The porosity of the backing sheet 10 is important because it provides openings for receiving the hydrocolloidal medication-containing reservoir and it helps to assure that the patch is non-occlusive to the skin. The infusion of the pressure-sensitive hydrocolloidal medication-containing reservoir into the backing sheet 10 is accomplished by controlling manufacturing parameters so as to keep the hydrocolloid sufficiently fluid to prepenetrate the backing sheet 10 in spite of its tendency to thicken rapidly when applied. In order to prevent the consistency of the hydrogel from building too fast, *i.e.*, becoming too viscous to properly penetrate the backing sheet 10, a continuous processing mixer 16 (Fig. 1) which includes rotating auger 18 is chilled to help remove heat produced during mixing and keep the hydrogel cool until applied to the backing 10. This can be accomplished by providing the processing mixer 16 with a cooling jacket through which a coolant such as a chilled mixture of water and ethylene glycol is passed during operation. The components of the hydrogel are continuously added to the mixer 16 during operation. While any suitable mixer 16 can be used, one suitable mixer is a 12.7 cm continuous processing mixer manufactured by Teledyne Readco Company of York, Pennsylvania. The coolant passed through the processing mixer 16 can be maintained at about 0°C. The temperature of the fluid hydrogel 20 as it flows onto the exposed surface of the backing sheet 10 is important for controlling the infiltration of the coating into the backing sheet 10. The coolant will, under typical operating conditions, keep the extruded hydrogel 20 at a temperature of about 9°C to 14°C as it comes into contact with the backing 10. If deeper penetration is desired, the temperature of the hydrogel is lowered to about 9°C for a typical hydrogel formulation. If less penetration is wanted, the temperature is raised closer to 15°C.

The hydrogel produced by the processing mixer 16, which is in a chilled fluid condition, is expelled at 20 onto the exposed upper surface of the backing sheet 10 adjacent to a knife blade 22 of a knife coater which is held in spaced relationship above a rotatable support roll 23. The distance between the knife 22 and the roll 23 is controlled in any suitable manner, as by means of adjustment screws (not shown) or, if desired, the desired gap or spacing between the knife 22 and roll 23 can be preset to accommodate the backing sheet 10 and the thickness of the hydrogel coating 24 that is being applied to the exposed surface of the backing sheet 10.

In accordance with the invention, the medication-containing hydrogel 20 is applied so as to penetrate a substantial portion of the backing sheet 10, *e.g.*, typically between one-fourth to nine-tenths the thickness of the backing sheet 10. The penetration of the coating 24 into the backing 10 can be seen in Fig. 5. In this case the hydrogel coating 24 has penetrated about three-fourths of the way through the backing sheet 10 to provide an upper, *i.e.*, internal layer 24a of hydrocolloidal material within the pores between the fibers making up the porous backing sheet 10. The hydrogel material thus includes two layers as seen in Fig. 5; the external coating layer 24 with an exposed pressure-sensitive surface 24b and the upper internal portion 24a which infiltrates and becomes solidified within the backing in the interstices between the fibers that make up the porous backing sheet 10.

In one product with very good characteristics the backing sheet 10 is 0.14 mm in thickness and the external part of the coating layer 24 is 0.2 mm in thickness to provide a combined thickness for the patch when applied to the body of 0.34 mm. The external hydrogel layer 24 is purposely maintained relatively thin. The hydrocolloidal adhesive reservoir infiltrates into the backing to a depth of about 0.05 mm to 0.13 mm to provide a total hydrocolloid layer, including both the internal and external portions, of about 0.25 mm to 0.33 mm. Because of its thickness, the medication-containing reservoir provides a very adequate supply of medication to assure sustained release of the medication over an extended period of time, *e.g.*, six to eight hours or more. During use, the medication in the internal reservoir portion 24a stored within the backing sheet 10 migrates from within the backing sheet 10 through the external coating layer 24 and then passes through the skin to provide sustained release of the medication into the body of the patient.

After the hydrogel layer 24 is applied to the backing 10, the backing sheet continues moving toward the right as seen in Fig. 1 into close proximity with an oven or heater, in this case a radiant electric heater 25 which radiates heat onto the hydrogel coating layer 24, raising its temperature to about 60°C and causing it to cure, *i.e.*, to set up as a solid that is sufficiently stable to maintain its own shape and resist flow during storage or use. Once the heater 25 has warmed the hydrogel coating 24, it will be solidified and dimensionally stable. If curing is conducted without the application of heat, *e.g.*, at room temperature, it will take longer than when heat is used. A liner sheet 26 such as polyethylene coated paper is then applied

continuously by pressing it onto the exposed surface of the hydrogel layer 24 as the liner sheet 26 passes beneath a rotating roll 28. The assembled laminate 34 then moves further toward the right in the figure where a die press 30 stamps separate patches 32 from the sheet material.

The hydrogel 20, 24 comprises a hydrocolloidal dispersion of a hydrophilic natural or synthetic gel-forming polymer, a hydrophilic humectant, a biomedically active substance or medication, *i.e.*, a medication, and a hydrophilic adhesive substance such as an aqueous dispersion of an acrylic adhesive.

The polymer can comprise a natural gum such as gum karaya, gum acacia, locust bean gum, guar gum, or other polysaccharide as well as synthetically formulated polysaccharides, *e.g.*, modified guar gum, maltodextrin, or celluloses such as carboxymethyl cellulose and carboxypropyl cellulose. The polymer can also comprise a synthetic polymer such as polyacrylamide and its congeners or polyacrylic acid. Polyacrylamide is sold under the trademark Polytec 31x by Tecna Corp., Belleville, New Jersey.

The humectant can comprise a polyhydric alcohol such as glycerol, propylene glycol, ethylene glycol, or sorbitol.

The adhesive can comprise any suitable biocompatible hydrophilic adhesive such as a resin emulsion adhesive, *e.g.*, an acrylate emulsion adhesive or a copolymer of vinyl acetate and dioctyl maleate. The most outstanding results have been achieved with an acrylic emulsion adhesive. Other hydrophilic adhesives that can be used include an acrylic ester copolymer and a vinyl acetate resin.

Any of a variety of topical medications can be used in accordance with the present invention. The medications can be selected from a topical analgesic, anti-pruritic agent, anti-inflammatory agent, anesthetic agent, keratolytic agent and rubrefacient agent. When the patch is used as an analgesic, the analgesic can include trolamine salicylate, methyl salicylate, menthol, camphor, eucalyptus oil, spearmint oil, or a combination thereof. In other applications, the medication can include anti-pruritic agents or anti-inflammatory agent such as hydrocortisone, or anesthetic agents such as benzocaine or lidocaine. Also included are non-steroidal anti-inflammatory agents such as ibuprofen, especially the S-isomer of ibuprofen. Other medications that can be used include keratolytic agents such as salicylic acid, and rubrefacient agents such as capsicum.

In Fig. 2 the finished patch 32 is seen applied to the surface of the body with the backing 10 exposed and the pressure-sensitive hydrogel layer 24 bonded to the skin.

In Fig. 3 is shown a package containing the finished patch 32 as it appears during shipment and storage. The package 36 comprises a pouch including lower and upper layers of paper 35, 37 or other suitable packaging material such as metal foil coated paper which is sealed to itself along its edges, *e.g.*, at 36a, 36b to provide a sealed pouch containing the finished patch 32.

As shown in Figs. 4 and 5, the finished patch 32 includes the porous backing 10, the hydrogel coating including the lower, *i.e.*, external hydrogel coating layer 24 and the upper or internal portion 24a that permeates the backing 10. The upper surface 26a of the liner sheet 26 is a release surface for facilitating its removal. Before use, the liner sheet 26 is removed by pulling it off the patch as shown at the right in Fig. 4 to expose the pressure-sensitive surface of the layer 24 which is then applied to the skin as shown in Fig. 2.

During use, the upper or internal reservoir portion 24a that infiltrates the backing 10 and is solidified therein serves to store the medication within the backing 10 so that the medication migrates over time from its location at 24a within the backing 10 through the external coating layer 24 and then passes through the skin to provide sustained release of the medication into the body of the patient.

The porosity of the backing 10 combined with the water compatibility of the hydrocolloidal dispersion also makes the patch non-occlusive so that moisture from the body can evaporate through the patch into the atmosphere. The moisture vapor transmission rate (MVTR) of the skin alone under various conditions is typically from about 70 to about 149 g/m²/24hr while the medication applying patch of the present invention is about 612 to 1952 g/m²/24hr. This shows that the invention is non-occlusive because in a given period of time about 8 to 14 times more moisture vapor is transmitted through the patch of the present invention than through the skin. Prior medication-applying patches that employed a rubber backing allow virtually no moisture evaporation from the skin. By contrast, the non-occlusive patch of the present invention will not interfere with moisture evaporation from the skin. This is important because the evaporation of moisture from the skin helps the skin to act in its normal capacity as a barrier to externally applied compounds which, if absorbed in excessive amounts, can produce toxic reactions or skin irritation. The invention thus enables the barrier function of the *stratum corneum* to be maintained.

When used as an analgesic patch, the present invention provides outstanding results in relieving pain such as arthritis pain and backache pain, as well as muscular aches and strains. Because of the thinness of the patch, it is perceived as being more comfortable, more flexible, less obtrusive and is more acceptable to the patient. The backing 10 is rendered so translucent by infiltration of the hydrocolloidal gel that the patch is very inconspicuous on the skin. The entire thickness of the analgesic patch is about 0.34 mm.

The invention will be better understood by reference to the following examples:

EXAMPLES

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Example Number	Percentage by Weight	Component	Example Number	Percentage by Weight	Component
1	31.8	Glycerin	7	29	Glycerin
	0.2	Quaternium-15 ¹		16	Polytec 31x ⁵
10	21	Propylene Glycol		30	Propylene Glycol
	1	Hydrocortisone		1	Hydrocortisone
	25	Karaya		12	Lodex ⁶
	21	HB Fuller 3120z ²		4	H ₂ O (deionized)
				8	HB Fuller 3120z ²
2	31.8	Glycerin	8	30.8	Glycerin
15	0.2	Quaternium-15 ¹		15.4	Polytec 31x ⁵
	21.5	Propylene Glycol		22.8	Propylene Glycol
	0.5	Hydrocortisone		8	Lidocaine
	25	Karaya		12	Lodex ⁶
	21	BF Goodrich 26171 ³		3	H ₂ O (deionized)
20				8	HB Fuller 3120z ²
3	27.72	Glycerin	9	30.8	Glycerin
	0.64	Quaternium-15 ¹		12	Karaya
	24.5	Propylene Glycol		6.4	Lodex ⁶
	0.5	Hydrocortisone		8	34x ⁴
25	24.64	Karaya		29.8	Propylene Glycol
	21	BF Goodrich 26222 ³		1	Capsicum
4	27.72	Glycerin		12	Flexcyl 1615 ⁷
	0.64	Quaternium-15 ¹	10	30.8	Glycerin
	24.64	Propylene Glycol		12	Karaya
	1	Hydrocortisone		5.4	Lodex ⁶
30	25	Karaya		9	34x ⁴
	21	BF Goodrich 26171 ³		25.8	Propylene Glycol
5	33	Glycerin		12	HB Fuller 3120z ²
	18	Karaya		5	Benzocaine
	9	34x ⁴	11	31.4	Glycerin
35	0.5	Hydrocortisone		12.6	Karaya
	21.5	Propylene Glycol		5.2	Lodex ⁶
	18	BF Goodrich 26171 ³		8	34x ⁴
6	14	Methyl Salicylate		29.8	Propylene Glycol
	4	Camphor		1	Hydrocortisone
40	6	Menthol		12	HB Fuller 3120z ²
	76	BF Goodrich 26222 ³			

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Example Number	Percentage by Weight	Component	Example Number	Percentage by Weight	Component
5	12	14 Methyl Salicylate	19	15.6	Methyl Salicylate
	4	Camphor		6.8	Camphor
	6	Menthol		4.8	Menthol
	38	BF Goodrich 26171 ³		30	BF Goodrich 26334 ³
	38	BF Goodrich 26415 ³		43	BF Goodrich 26222 ³
10	13	14 Methyl Salicylate	20	15	Trolamine Salicylate
	4	Camphor		10	Menthol
	6	Menthol		34	BF Goodrich 26171 ³
	45	BF Goodrich 26415 ³		41	BF Goodrich 26222 ³
	31	BF Goodrich 26222 ³			
15	14	17.4 Methyl Salicylate	21	20.3	Methyl Salicylate
	7.5	Camphor		6.6	Menthol
	5.1	Menthol		32.5	BF Goodrich 26171 ³
	70	BF Goodrich 26415 ³		40.6	BF Goodrich 26222 ³
20	15	15.6 Methyl Salicylate	22	15	Methyl Salicylate
	6.8	Camphor		10	Menthol
	4.6	Menthol		29	BF Goodrich 26171 ³
	25	BF Goodrich 26171 ³		46	BF Goodrich 26222 ³
25	16	19.8 Karaya	23	23	Karaya
	36.6	Glycerin		34	Glycerin
	15.8	Methyl Salicylate		11.5	Methyl Salicylate
	2	Spearmint Oil		3	Menthol
	25.8	HB Fuller 3120z ²		3	Camphor
30	17	19 Karaya	24	1.5	Spearmint Oil
	37	Glycerin		23	Avery AE259 ⁸
	16	Methyl Salicylate			
	2	Spearmint Oil		22.5	Karaya
	13	BF Goodrich 26171 ³		36	Glycerin
35	13	BF Goodrich 26415 ³		16	Methyl Salicylate
				3	Spearmint Oil
				8	BF Goodrich 26222 ³
				14.5	BF Goodrich 26171 ³
40	18	20 Karaya		25	22.5 Karaya
	37	Glycerin		35.9	Glycerin
	8	Methyl Salicylate		11.8	Methyl Salicylate
	8	Trolamine Salicylate		3.1	Camphor
	2	Spearmint Oil		3.1	Menthol
45	12.5	BF Goodrich 26415 ³		1.6	Spearmint Oil
	12.5	BF Goodrich 26222 ³		22	BF Goodrich 26415 ³
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	Example Number	Percentage by Weight	Component	Example Number	Percentage by Weight	Component
5	26	24	Karaya	32	23.5	Karaya
		34	Glycerin		33.5	Glycerin
		15	Methyl Salicylate		15.7	Methyl Salicylate
		2	Spearmint Oil		2.8	Spearmint Oil
		12.5	BF Goodrich 26171 ³		9.1	BF Goodrich 26222 ³
		12.5	BF Goodrich 26334 ³		15.4	BF Goodrich 26171 ³
10	27	21	Karaya	33	22.6	Karaya
		38	Glycerin		35.9	Glycerin
		15	Methyl Salicylate		6	Methyl Salicylate
		2	Spearmint Oil		5.9	Trolamine Salicylate
		12	BF Goodrich 26415 ⁵		3.2	Camphor
		12	BF Goodrich 26334 ³		3.2	Menthol
15	28	23	Karaya		1.5	Spearmint Oil
		37.5	Glycerin		7.5	BF Goodrich 26222 ³
		13.8	Methyl Salicylate		14.2	BF Goodrich 26171 ³
		1.7	Spearmint Oil	34	22	Karaya
		12	BF Goodrich 26171 ³		35	Glycerin
20		12	Aroset 1196 ⁶		16	Methyl Salicylate
	29	22	Karaya		4	Menthol
		36	Glycerin		6	Camphor
		14.2	Methyl Salicylate		2	Spearmint Oil
		1.8	Spearmint Oil		9	BF Goodrich 26415 ³
25		3	Camphor		6	BF Goodrich 26171 ³
		11.5	Aroset 1196 ⁹	35	20	Karaya
		11.5	BF Goodrich 26222 ³		33.8	Glycerin
	30	22	Karaya		0.2	Quaternium-15 ¹
30		35	Glycerin		16	Methyl Salicylate
		12	Methyl Salicylate		4	Menthol
		3.2	Methol		6	Camphor
		3.2	Camphor		1.5	Spearmint Oil
		1.6	Spearmint Oil		12	BF Goodrich 26222 ³
		11	Avery AE259 ⁸		6.5	BF Goodrich 26171 ³
35		12	BF Goodrich 26171 ³	36	54	Glycerin
	31	54	Glycerin		26	Karaya
		26	Karaya		5	BF Goodrich 26222 ³
		10	Flexcryl 1615 ⁷		5	BF Goodrich 26171 ³
		3.3	Eucalyptus Oil		6.7	Menthol
40		6.7	Menthol		3.3	Eucalyptus Oil

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	Example Number	Percentage by Weight	Component	Example Number	Percentage by Weight	Component
5	37	53	Glycerin	44	49	Glycerin
		25	Karaya		28	Karaya
		9.5	Flexcryl 1615 ⁷		15	BF Goodrich 26171 ³
		8.4	Menthol		6.7	Menthol
		4.1	Eucalyptus Oil		3.3	Eucalyptus Oil
10	38	46.5	Glycerin	45	48	Glycerin
		8.4	Menthol		24.5	Karaya
		4.1	Eucalyptus Oil		15	BF Goodrich 26171 ³
		26	Karaya		8.4	Menthol
		15	Flexcryl 1615 ⁷		4.1	Eucalyptus Oil
15	39	16.8	Menthol	46	49.3	Glycerin
		8.2	Eucalyptus Oil		23.2	Karaya
		25	Avery AE259 ⁸		15	BF Goodrich 26334 ³
		34	Glycerin		8.4	Menthol
		16	Karaya		4.1	Salicylic Acid
20	40	54	Glycerin	47	50	Glycerin
		26	Karaya		25	Karaya
		10	BF Goodrich 26222 ³		15	BF Goodrich 26171 ³
		6.7	Menthol		6.7	Menthol
		3.3	Eucalyptus Oil		3.3	Eucalyptus Oil
25	41	54	Glycerin	48	47	Glycerin
		26	Karaya		20.5	Karaya
		10	BF Goodrich 26171 ³		15	BF Goodrich 26415 ³
		6.7	Menthol		11.7	Menthol
		3.3	Eucalyptus Oil		5.8	Eucalyptus Oil
30	42	54	Glycerin	49	49.3	Glycerin
		31	Karaya		23.2	Karaya
		5	Flexcryl 1615 ⁷		15	BF Goodrich 26171 ³
		6.7	Menthol		8.4	Menthol
		3.3	Eucalyptus Oil		4.1	Eucalyptus Oil
35	43	54	Glycerin	50	47	Glycerin
		36	Karaya		24.8	Karaya
		6.7	Menthol		6.7	Menthol
		3.3	Eucalyptus Oil		3.3	Eucalyptus Oil
					18.2	Aroset 1196 ⁹

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Footnotes:

- 1 Quaternium-15 is a preservative comprising azoniaadamantane chloride by Dow Chemical of
5 Palatine, IL.
- 2 HB Fuller 3120z is a residual vinyl acetate monomer resin emulsion in water by HB Fuller of
Vadnais Heights, MN.
- 3 BF Goodrich 26171, 26222, 26334 and 26415 are acrylic ester copolymers of anionic emulsion
10 adhesives by BF Goodrich of Brecksville, OH.
- 4 34x is an anionic polyacrylamide by Tecna Corporation of Belleville, NJ.
- 5 Polytec 31x is a non-ionic polyacrylamide by Tecna Corporation of Belleville, NJ.
- 6 Lodex is a carbohydrate comprising Malto Dextrin by American Maize-Product Company of
15 Hammond, IN.
- 7 Flexcryl 1615 is an adhesive of vinyl acetate / dioctylmaleate copolymer by Air Products and
Chemical Inc of Allentown, PA.
- 8 Avery AE259 is an acrylic polymer fatex adhesive by Avery Chemical of Mill Hill, PA.
- 9 Aroset 1196 is an acrylic polymer adhesive by Ashland Chemical of Columbus, OH.

Many variations of the present invention within the scope of the appended claims will be apparent to
25 those skilled in the art once the principles described herein are understood.

Claims

- the internal portion of the hydrophilic hydrocolloidal reservoir which infiltrates the backing is solidified
30 within the pores and interstices within the backing so that the reservoir and the backing are unified such
that the backing acts as a storage location for the medication-containing reservoir,
the solidification of the gel reservoir is delayed until after the application thereof to the porous backing
layer,
whereby medication within the reservoir migrates over time from within the backing through the lower
35 coating layer and passes through the skin to provide sustained release of the medication into the body of
the patient from the porous backing layer.
2. The adhesive patch of claim 1 wherein the porous backing layer is a nonwoven fabric comprising water
insoluble polymeric fibers with spaces therebetween.
 3. The adhesive patch of claim 2 wherein the nonwoven fabric comprises a mixture of polyester fibers and
40 cotton fibers.
 4. The adhesive patch of claim 1 wherein the reservoir comprises a hydrocolloidal dispersion of a
hydrophilic natural or synthetic gel-forming polymer, a liquid humectant, an adhesive with said biomedically
active medication dispersed therein and the natural or synthetic gel-forming polymer comprises a member
selected from the group consisting of gum karaya, gum acacia, locust bean gum, guar gum, modified guar
45 gum, maltodextrin, carboxymethyl cellulose, carboxypropyl cellulose, polyacrylamide and its congeners, and
polyacrylic acid.
 5. The adhesive patch of claim 1 wherein the reservoir contains a humectant which comprises a polyhydric
alcohol.
 6. The adhesive patch of claim 5 wherein the polyhydric alcohol comprises a member selected from the
50 group consisting of glycerol, propylene glycol, ethylene glycol, and sorbitol.
 7. The adhesive patch of claim 1 wherein the adhesive is a resin emulsion adhesive.
 8. The adhesive patch of claim 7 wherein the resin emulsion adhesive comprises a member selected from
the group consisting of acrylate emulsion adhesive, an acrylic ester copolymer, a vinyl acetate resin, and
copolymer of vinyl acetate and dioctyl maleate.
 9. The adhesive patch of claim 1 wherein the medication comprises one or more of the following: trolamine
55 salicylate, methyl salicylate, menthol, camphor, eucalyptus oil, spearmint oil, hydrocortisone, benzocaine,
lidocaine, ibuprofen, salicylic acid, and capsicum.

10. The non-occlusive adhesive patch of claim 1 wherein the internal portion of the adhesive reservoir penetrates the porous backing layer to a depth of about at least one-fourth the thickness of the backing layer.

11. The non-occlusive adhesive patch of claim 1 wherein the internal portion of the adhesive reservoir penetrates the porous backing layer to a depth of about nine-tenths the thickness of the backing layer.

12. A method of forming a non-occlusive medication-containing adhesive patch to be applied to the skin for releasing a medication into the body of a patient comprising,

providing a porous backing layer of flexible water insoluble polymeric sheet material,

forming a dispersion of a polymer comprising an adhesive and a biomedically active medication to

provide a pressure-sensitive hydrocolloidal gel reservoir,

expelling the hydrocolloidal gel onto the backing layer while maintaining the dispersion in a chilled condition,

the hydrocolloidal gel being chilled to a temperature effective to maintain the dispersion sufficiently fluid when applied to the backing layer to penetrate the backing layer to a depth of at least about one-fourth the thickness of the backing layer,

forming the hydrocolloidal gel into a coating on the backing, said coating having a flat, exposed, pressure-sensitive surface for bonding to the skin,

said pressure-sensitive hydrocolloidal gel reservoir thereby having two portions including:

(a) an external coating layer with said exposed surface for bonding to the skin, and

(b) an internal portion infiltrated within the pores of the backing layer, and allowing the hydrocolloidal gel to cure in place upon and within the porous backing layer.

13. The method of claim 12 wherein the curing is accelerated by heating the hydrocolloidal gel after the gel has infiltrated into the pores of the backing layer.

14. The method of claim 12 wherein the coating of the hydrocolloidal gel is formed by a knife coater to provide said pressure-sensitive surface for bonding to the skin.

15. The method of claim 14 wherein a sheet of a liner paper is applied to the pressure-sensitive surface of the hydrocolloidal gel coating to protect the same during shipment and storage.

16. The method of claim 12 wherein the dispersion is formed continuously within a processing mixer and is then applied as a continuous stream on a moving strip of said backing layer and a web of liner paper having a release surface is applied continuously to the exposed pressure-sensitive surface of the hydrocolloidal gel coating to protect the coating during shipment and storage, and said adhesive patches are cut therefrom.

17. The method of claim 16 wherein the hydrocolloidal gel reservoir is infiltrated into the porous backing layer to a depth of between about one-fourth and nine-tenths the thickness of the backing layer and is solidified within the pores of the backing layer to unify the backing layer and the coating such that the backing layer acts as a storage location for the medication-containing hydrocolloidal gel reservoir.

